Remarks

Claims 26-35 are pending in the application. Applicants have canceled claims 26-35 without prejudice to later claiming the subject matter in these claims.

New claims 36-50 have been added without introducing new matter. Support for the new claims can be found throughout the specification, for example, at pages 3 to 7.

Rejection of Claims 26-30 and 32-33 under 35 USC 102 over Platz

Claims 26-30 and 32-33 were rejected allegedly as being anticipated under 35 USC 102(e) over U.S. Patent 6,582,728 (hereinafter "Platz"). Without conceding the basis for the rejection, claims 26-35 have been canceled while reserving the right to later claim the subject matter in these claims. The rejection therefore is moot as to these claims. Following are remarks respecting new claims 36-50.

New claims 36-50 are novel over Platz at least for the reason that Platz does not expressly or inherently disclose each element of Applicants' claimed invention.

Platz teaches a dispersible pharmaceutical-based dry powder formulation useful for pulmonary administration. The examiner cites, *inter alia*, Example 2 in support of the rejection. Example 2 teaches a formulation prepared by a 2-step process: step A discloses an *in-process* solution comprising 5% PTH(1-34) (.375 mg/ml), mannitol (6.06 mg/ml), and citrate buffer (1.04 mg/ml), pH 6.3; step B discloses further processing the in-process solution to produce the finished dried product, *i.e.* a dried powder for pulmonary use.

Claims 36-50 are clearly not anticipated by Platz. Claims 36-46 are novel at least for the following reasons. First, Platz does not teach use of acetate buffer. Second, Platz does not teach a parenterally acceptable preservative. Platz discloses an in-process solution, which immediately precedes a step of spray-drying to produce a dried powder for *pulmonary* use. Thus, not only does Platz not disclose a parenteral preservative, but owing to the intended purpose of the Platz formulation, there would have been no reason to do so. Third, the disclosure provided by Platz in Example 2 does not clearly and unambiguously teach that the in-process solution is in a sterile form and ready for parenteral administration to a human patient, as required by Applicants' claims.

In addition, claims 42, 43, and 46 are novel over Platz for the additional reason of being directed to a concentration of 250 ug/ml PTH(1-34). Platz does not teach this concentration. Therefore, claims 36-46 are not anticipated by Platz.

Claims 47-50 are also novel over Platz at least for the reasons that claims 47-50 are limited to *sealed* vials containing a ready to administer PTH formulation of defined composition. As previously described, the claimed constituents of Applicants' claimed formulation are not clearly and unambiguously described by Platz. For example, Platz does not teach a sterile, ready to administer PTH solution comprising acetate or tartrate. Nor does Platz teach a parenterally acceptable preservative. Nor does Platz teach the formulations claimed by Applicants in a sealed vial. To the extent Platz teaches a solution, the solution must be in an open container in order to be spray-dried. Thus Platz does not anticipate claims 47-50.

Applicants respectfully submit that Platz does not anticipate any of claims 36-50. Applicants request withdrawal of the rejection.

Rejection of Claims 26-31 and 33 under 35 USC 102 over Holthuis

Claims 26-31 and 33 were rejected allegedly as being anticipated under 35 USC 102(b) over U.S. Patent 5,496,801 (hereinafter "Holthuis"). Without conceding the basis for the rejection, claims 26-35 have been canceled while reserving the right to later claim the subject matter encompassed by these claims. The rejection is therefore moot as to the cancelled claims. Applicants provide remarks directed to new claims 36-50 in the following paragraphs.

New claims 36-50 are novel over Holthuis for the reason that Holthuis does not expressly or inherently teach each element of Applicants' claimed invention. First, Holthuis teaches a freeze-dried formulation of parathyroid hormone, that requires use of a "non-volatile" buffer such as citrate or phosphate. Holthuis specifically excludes volatile buffers such as acetate, which are unsuitable for freeze-drying.

> The buffering agent incorporated in the preparation of the present invention, in addition to being acceptable pharmaceutically, is necessarily a non-volatile buffering agent, i.e. one that is not volatilized during the freeze-drying process . . . . Buffering agents used previously in PTH preparations, such as acetic acid, were found to volatilize at differential rates during the freeze-drying process, leading not only to inconsistent product but also to the loss of buffering agent, and hence inconsistent pH levels in the reconstituted product.(*See* Col.3, Lines 48-58; Col.4, Lines 3-8).

As such, Holthuis does not anticipate new claims 36-46, at least for the reason that the claims are limited to acetate buffer.

Second, Applicants claim a *sterile*, ready to administer solution formulation. Holthuis does not clearly and unambiguously teach that the in-process solution, which precedes the step of freeze-drying, is in a sterile form. The example at Column 6 teaches that an in-process solution is produced in stages. First, two solutions are produced, one of 5% mannitol and 10 mM citric acid; the other of 5% mannitol and 10 mM citrate. The disclosure does not specify, nor would it be inherently required, that the citric acid/citrate solutions are in a sterile form. Indeed, the example goes on to suggest otherwise. "For freeze-drying, solutions containing PTH at each of the prepared concentrations were aseptically filled . . . into glass vials." (Col 6, lines 31-34). It therefore cannot be said that the in-process solution is unambiguously sterile.

Thirdly, claims 42, 43, and 46 are further novel over Holthuis for the reason that Holthuis does not disclose the claimed concentration of PTH(1-34) of 250 ug/ml. Holthuis teaches in-process solutions of *PTH(1-84)* [*not* PTH(1-34)] at a concentration of 25 ug/ml to 250 ug/ml (Col. 4, lines 35-39). Holthuis teaches that concentration ranges for fragments of PTH (*i.e.* other than PTH(1-84)) are determined on a molar equivalency basis (see Col 4, lines 39-42). *If* one assumes a rough approximation of the molar equivalency of PTH(1-34) to PTH(1-84) to be 0.43[1], then 250 ug/ml PTH(1-84) would roughly approximate 107 ug/ml PTH(1-34). Thus, Holthuis does not teach Applicants' claimed concentration of 250 ug/ml PTH(1-34). As such Holthuis does not anticipate claims 42, 43, and 46.

Claims 47-50 are also novel over Holthuis. Claims 47-50 are directed at *sealed* vials containing a ready to administer PTH solution of the claimed composition and concentration ranges, for parenteral administration. Holthuis does *not* disclose a *sealed* vial containing a ready for parenteral administration pharmaceutical composition comprising PTH(1-34). To the extent Holthuis teaches a vial containing a solution, it is either (1) an in-process solution prior to freeze-drying, or (2) a reconstituted solution. In the former case, the vial must be open in order to allow for subsequent freeze-drying. Morever, as stated in the attached declaration by Daniel Lynch, "A liquid prepared by reconstituting a freeze-dried powder is not referred to as "ready to administer." Furthermore, a reconstituted solution in a vial is the result of puncturing the seal in order to introduce water or buffer to reconstitute a dried pellet. As such a vial containing a

[1] This assumes a molecular weight of 4117 for PTH(1-34) and 9500 for PTH(1-84).

reconstituted solution is not clearly and unambiguously sealed. Thus, claims 47-50 are novel over Holthuis.

Applicants respectfully submit that Holthuis does not anticipate any of Applicants' claims and therefore request withdrawal of the rejection.

Rejection of Claims 26-35 under 35 USC 103

Claims 26-35 were rejected for alleged obviousness over Holthuis in view of Martin et al. (hereinafter "Martin"). The rejection states, "The difference between the prior art [*i.e.* Holthuis] and the instant application is that the reference does not teach the use of benzyl alcohol in the composition. However, Martin et al. illustrates that when benzyl alcohol was used in a PTH formulation . . . binding to the PTH-receptor was increased by 25% . . . . Therefore it would have been obvious . . . to incorporate benzyl alcohol into a formulation of PTH . . . ."

Without conceding the basis for the rejection Applicants have canceled claims 26-35, thereby rendering the rejection moot as to these claims. Applicants reserve the right to later rebut the allegation and claim the subject matter in these claims. Applicants provide remarks directed to new claims 36-50 in the ensuing paragraphs of this section.

The factual inquiries for determining obviousness under Section 103 are: (1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims at issue; and (3) determine the level of ordinary skill in the pertinent art. *Graham v. John Deere*, 148 U.S.P.Q. 459 (1966). The PTO bears the initial burden of establishing a *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984). To establish a *prima facie* case of obviousness, the Examiner must show (1) some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references to achieve the claimed invention. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); (2) from the vantage point of the skilled artisan at the time of the invention, the proposed modification of the prior art must have had a reasonable expectation of success based on the disclosure in the prior art. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991); and (3) the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed.

Cir. 1991). Applicants respectfully submit that the rejection does not set forth a *prima facie* case of obviousness.

First, there is no evidence of record that a skilled artisan would have been motivated to modify the cited prior art references to achieve Applicants' claimed invention, or that there would have been a reasonable expectation of success in doing so. If anything the evidence is decidedly in the opposite direction. Additionally, the cited art fails to teach or suggest all the limitations of Applicants' claims.

Applicants' claims relate to ready to administer pharmaceutical solution formulations comprising PTH(1-34). Holthuis taught that there was a significant problem in stably formulating PTH, namely its well-known sensitivity to chemical degradation and concurrent loss of biological activity. In this regard, Holthuis mentions oxidation at Met residues. Unlike Applicants, Holthuis taught that this problem was to be solved by freeze-drying a formulation because freeze-drying was believed to be the best means to reduce the rate of chemical degradation and thereby produce a storage stable PTH formulation.

Unlike Holthuis, Applicants' claimed invention does not involve freeze-drying or reconstitution as a means to solve the problem associated with PTH instability. Applicants' claims are directed at a "ready to administer" solution formulation that has not been freeze-dried or reconstituted. There is not the slightest hint or suggestion in Holthuis that PTH could be stably formulated as a ready to administer solution.

Applicants' claims would not have been obvious over Holthuis at least for the following reasons. First, claims 36-46 are directed (1) at a ready to administer PTH solution formulation that comprises acetate buffer, and (2) a method of preparing same. Holthuis decidedly taught away from use of volatile buffers such as acetate because of their volatility and incompatability with freeze-drying (*See e.g.* Col 3, lines 48-57). Thus, Holthuis decidedly taught away from use of acetate. Applicants respectfully submit that at least for these reasons claims 36-46 (which are limited to acetate) would not have been obvious over Holthuis, alone or in combination with Martin.

New claims 47-50 relate to *sealed* vials containing a ready to administer solution that has not been reconstituted in the vial. As noted *supra*, Holthuis unambiguously teaches a freeze-dried product. Freeze-drying of an in-process solution cannot take place if a vial containing the solution is sealed. Thus, the vials disclosed in Holthuis prior to freeze-drying must be unsealed. Moreover, as discussed above, to the extent Holthuis

teaches a vial containing a reconstituted solution, the vial must be punctured to allow for reconstitution, and it is not unambiguously the case that such a vial remains sealed. Thus, claims 47-50 would not have been obvious over Holthuis.

Martin adds nothing to Holthuis to suggest Applicants' claimed invention. Martin relates to basic research on the affect of benzyl alcohol on the enzymatic activity of adenylate cyclase. Nothing in Martin directly relates to pharmaceutical formulations, nor to the subject matter of Applicants' claimed invention. Hence, even if there were motivation to combine Martin and Holthuis, which Applicants deny, the combination fails to suggest Applicants' claimed invention.

Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 26-30 and 32-35 under 35 USC 103

Claims 26-30 and 32-35 were rejected for alleged obviousness over Platz in view of Martin. The rejection states, "The difference between the prior art [*i.e.* Platz] and the instant application is that the reference does not teach the use of benzyl alcohol in the composition. However, Martin et al. illustrates that when benzyl alcohol was used in a PTH formulation . . . binding to the PTH-receptor was increased by 25% . . . . Therefore it would have been obvious . . . to incorporate benzyl alcohol into a formulation of PTH . . . ."

Without conceding the basis for the rejection Applicants have canceled claims 26-35, thereby rendering the rejection moot as to these claims. Applicants reserve the right to later rebut the argument and/or claim the subject matter in these claims. In the following paragraphs Applicants provide remarks respecting new claims 36-50.

Applicants respectfully submit that a *prima facie* case of obviousness over the combination of references has not been made [*See e.g.* MPEP §706.02(j)]. First, there would have been no motivation to combine Platz and Martin. Platz relates to pharmaceutical formulations for pulmonary administration while Martin relates to basic research on the affect of benzyl alcohol on membrane fluidity, specifically to the effect on enzymatic activity of membrane-bound adenylate cyclase in dog kidney cells. Martin has nothing to do with pharmaceutical formulations *per se*, nor to Applicants' claims in particular, and there would have been no motivation to combine Platz with Martin.

But even *if* there were motivation to combine Platz and Martin, the combined teaching would not suggest Applicants' claimed invention. Claims 36-47 are directed at a ready to administer pharmaceutical composition comprising PTH(1-34) and a parenterally acceptable preservative for parenteral administration. As previously noted, Platz teaches a spray-dried formulation for pulmonary administration. In one example, Platz discloses an in-process solution comprising 375 ug/ml PTH(1-34), 0.6% (6.06 mg/ml) mannitol, and 1.04 mg/ml (3.6 mM) citrate buffer. Applicants respectfully assert that none of the claims are obvious over Platz alone or in combination with Martin at least for the following reasons. First, Platz teaches a formulation for pulmonary use. There was no teaching or suggestion in Platz, nor would there have been motivation, to include a parenteral preservative in the formulation taught by Platz. That would have been wholly outside the spirit and scope of the invention disclosed by Platz, namely a formulation for pulmonary administration. Second, there is no teaching or suggestion in Platz, taken alone or in combination with Martin, to direct a skilled artisan to Applicants' formulation, having the claimed components and concentrations. Thus, for example, Platz does not teach or suggest use of acetate buffer. Given Platz's intended purpose – to produce a dried formulation for pulmonary use, acetate would have been unacceptable for producing a dried product, owing to its known volatility and the resultant impact on pH.

Claims 47-50 are directed at sealed vials containing a ready to administer solution formulation comprising PTH(1-34). These claims are patentably distinguishable over Platz, alone or in combination with Martin. As previously noted, Platz teaches dried formulations for pulmonary administration. Platz does not teach or suggest vials containing a ready to administer pharmaceutical solution formulation for parenteral administration, let alone a ready to administer solution contained in *sealed* vials. Thus, claims 47-50 would not be obvious over Platz, alone or in combination with Martin.

Rejection of Claims 26-35 for Obviousness-Type Double Patenting

Claims 26-35 were rejected for alleged obviousness-type double patenting over U.S. Patent 6,770,623. Without conceding the basis for this rejection, and reserving the right to later rebuttal, Applicants submit herewith a terminal disclaimer pursuant to 37 CFR 1.321 (c) and 37 CFR 1.130(b), disclaiming any term of a patent granting on the instant application extending beyond the term of U.S. Patent 6,770,623. Applicants

respectfully request withdrawal of the rejection and passage of the case to issuance as soon as possible.

Applicants have successfully addressed each point of the rejection and with utmost respect request withdrawal of the rejection and passage of the case to issuance as soon as possible.

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